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TI Possible activation of auto-immune thyroiditis from continuous  
subcutaneous infusion of \*\*\*genapol\*\*\* -containing insulin.  
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AB A case of a type 1 diabetic woman with auto-immune thyroiditis is  
reported, in whom repeated exposure to insulin containing \*\*\*Genapol\*\*\*  
(R) (polyethylen-polypropylenglycol) over 3 years reproducibly parallels  
with an increase of serum TSH (thyroid-stimulating hormone) above the  
normal limit. Previously, adverse effects of \*\*\*Genapol\*\*\* (R) insulin

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## CASE REPORT

# POSSIBLE ACTIVATION OF AUTO-IMMUNE THYROIDITIS FROM CONTINUOUS SUBCUTANEOUS INFUSION OF GENAPOL-CONTAINING INSULIN

E. CHANTELAU

**SUMMARY** - A case of a type 1 diabetic woman with auto-immune thyroiditis is reported, in whom repeated exposure to insulin containing Genapol® (polyethylen-polypropylenglycol) over 3 years reproducibly parallels with an increase of serum TSH (thyroid-stimulating hormone) above the normal limit. Previously, adverse effects of Genapol® insulin have been related to its intraperitoneal application, and thought to be restricted to anti-insulin-immunity; activating effects on thyroid auto-immunity have been repeatedly disputed. We suggest that Genapol® insulin should be replaced by other insulin preparations with a better safety record.

**Key-words:** insulin treatment, adverse effects, insulin formulation, hypothyroidism, antibodies.

**RÉSUMÉ** - Possible activation d'une thyroïdite auto-immune par l'administration sous-cutanée continue d'insuline contenant du Genapol®.

Nous rapportons le cas d'une femme diabétique de type 1 avec thyroïdite auto-immune, chez qui l'exposition répétée à de l'insuline contenant du Genapol® (polyéthylène-polypropylenglycol) pendant trois ans était suivie de façon parallèle et reproductible par une augmentation de la TSH (thyroid-stimulating hormone) sérique au delà des taux normaux. Auparavant, des effets indésirables des préparations insuliniques contenant du Genapol® avaient été rapportés à la voie intrapéritonéale et supposés restreints à une immunité anti-insuline ; les effets activateurs sur l'auto-immunité thyroïdienne ont été très débattus. Nous suggérons que les insulines Genapol® soient remplacées par d'autres préparations insuliniques offrant plus de garanties de sécurité.

**Mots-clés :** traitement par insuline, effets secondaires, préparation insulinaire, hypothyroïdie, anticorps.

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**T**he human regular insulin preparation HOE 21 insulin (H-Tronin®, Hoechst Marion Roussel, Frankfurt/Germany) in a concentration of 400 units/ml (U400) contains the additive polyethylen-polypropylenglycol (Genapol®) as a stabilising agent [1, 2]. While it is undisputed that the intraperitoneal application of this insulin preparation increases anti-insulin immunity [3-6], its potential of inducing thyroid autoimmunity remains controversial [4]. The present observation in a type 1 diabetic patient with auto-immune thyroiditis indicates that long-term subcutaneous application of Genapol® containing insulin (H-Tronin Hoechst Marion Roussel, Frankfurt/Germany) can affect thyroid-stimulating hormone.

## CASE

A woman born 1959 was diagnosed with type 1 diabetes in 1982, and treated by continuous subcutaneous insulin infusion (CSII) since 1984. Subclinical auto-immune thyroiditis was detected in 1990 by ultrasound and blood chemistry; treatment was not required. Some years later, she obtained a H-Tron® insulin pump (Disetronic GmbH, Sulzbach/Germany) to be operated with cartridges of Genapol® containing H-Tronin® insulin U100. Between 1996 and 1999 she agreed to be assessed repeatedly for anti-thyroperoxidase (ATPO), anti-thyroglobulin (ATG), thyroid-stimulating hormone (TSH), triiodothyronine (T3) and free thyroxine (fT4). TSH, T3 and fT4 were measured by electrochemiluminescence immuno assay ECLIA (Elecsys® Boehringer Mannheim/Germany), with < 5% coefficient of variation in interassay precision, and lower detection limits of 0.014 uU/ml (TSH), 0.195 ng/ml (T3), and 0.23 pg/ml (fT4), respectively. ATPO and ATG were measured by enzyme-immunoassay (ES 700, Boehringer-Roche, Mannheim/Germany).

The patient voluntarily alternated twice from H-Tronin U100 insulin to Huminsulin® regular U100

(Lilly Deutschland GmbH, Bad Homburg/Germany), and back for several months. Huminsulin® regular is free from polyethylen-polypropylenglycol (Genapol®); to be used with the H-Tron® pump, it has to be drawn into cartridges by hand.

During 1996-1999, fluctuations in thyroid antibody concentrations were observed in relation to changing the insulin preparations, and fluctuations in fT4 and T3, which may be considered irrelevant (Table 1). However, with a latency of some months, slightly supranormal TSH normalised after changing the insulin preparation from H-Tronin® to Huminsulin®, and increased again above the normal range after changing back to H-Tronin®. This was also true for the re-exposition experiment (Fig. 1). Clinical signs of hypothyroidism were not observed.

## DISCUSSION

The data suggest that prolonged subcutaneous administration of human regular insulin containing Ge-

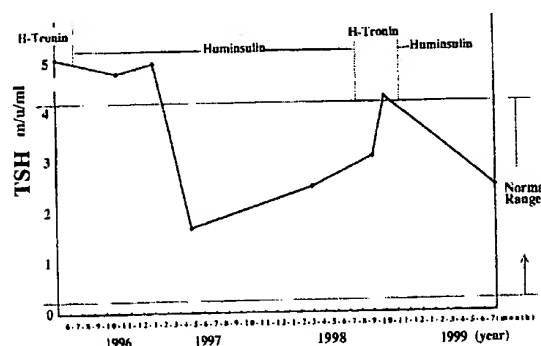


FIG. 1. Time course of fluctuations in thyroid-stimulating hormone (TSH) following changes from regular human H-Tronin insulin Hoechst (with Genapol®) to Huminsulin Lilly (without Genapol®) in a patient with auto-immune thyroiditis.

TABLE 1. Fluctuations in thyroid immunity and hormones over time, in relation to subcutaneous administration of regular human insulin with Genapol® (H-Tronin insulin Hoechst) or without Genapol® (Huminsulin Lilly) in a patient with auto-immune thyroiditis. TSH= thyroid-stimulating hormone, ATPO= anti-thyroperoxidase, ATG= anti-thyroglobulin, T3=triiodothyronine, fT4=free thyroxine, n.a.=not available.

	6/96	12/96	3/97	6/97	4/98	9/98	10/98	7/99
ATPO (<32 IU/ml)	614	532	382	514	268	420	330	339
ATG (<115 IU/ml)	164	115	n.a.	n.a.	118	125	123	141
T3 (0.8-2.0 ng/ml)	1.2	1.5	1.3	1.4	1.3	1.2	1.2	1.1
fT4 (9.1-19.1 pg/ml)	8.8	11.0	9.9	8.7	9.5	10.5	8.9	9.1
TSH (0.3-4.2 uU/ml)	5.1	4.8	5.0	1.7	2.5	3.4	4.3	2.5
	H-Tronin		Huminsulin		H-Tronin		Huminsulin	

napol® resulted in mildly supranormal concentrations of TSH, possibly due to an activation of the pre-existing auto-immune thyroiditis. TSH elevation normalised about 9 months after cessation of Genapol® insulin, and recurred about 5 months after re-exposition to Genapol® insulin. TSH normalised again, after Genapol® insulin was stopped again, suggesting a cause-effect-relationship rather than a spontaneous fluctuation.

Previously, adverse effects of Genapol® insulin were related to its intraperitoneal application, and thought to be restricted to anti-insulin-immunity; activating effects on thyroid auto-immunity have been repeatedly disputed [4]. However, the present data show that Genapol® insulin by subcutaneous application could have adverse effects on thyroid-stimulating hormone in certain patients with preexisting antithyroid antibodies. Thus, these effects may not necessarily be restricted to one mode of application of the insulin preparation, and to one particular autoimmune reaction, respectively.

The German Diabetes association and the manufacturer Hoechst Marion Roussel were already addressed in 1996 to issue a warning on the use of H-Tronin® insulin by diabetic patients with thyroid diseases; however, no action was taken, the patient information on H-Tronin® insulin was not changed.

In Germany, about 15 000 type 1 diabetic patients are currently being treated by CSII, the vast majority by H-Tron® pumps loaded with prefilled cartridges of H-Tronin® insulin (communication by the distributor). Up to 16% of type 1 diabetic patients suffer from autoimmune manifestations against the thyroid [7],

giving an estimated 2500 patients in Germany being exposed to unnecessary drug-induced activation of their thyroid diseases.

In consideration of the lacking evidence of any clinical benefit from using Genapol® insulin for pump treatment, at least for CSII treatment, and of the immunity problems previously related to Genapol® insulin [3-6], we suggest that Genapol® insulin should be withdrawn and replaced by other insulin preparations with a better safety record.

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